REMARKS

Claims 1-15 are pending in this application. Claims 16-28 have been canceled without prejudice or disclaimer and claims 1-15 have been amended by this amendment.

Regarding the Restriction Requirement

The Examiner has required restriction to either claims 1-15 (Group I) or Claims 16-28 (Group II). Applicants have already provisionally elected claims 1-13 (Group I of the previous restriction requirement), and the Examiner has rejoined claims 14 and 15 with Group I. Applicants here elect group I, claims 1-15, without traverse, and have canceled non-elected claims 16-28.

Claims 1-16 are objected to.

The objection is overcome by the amendments to claims 1-15, which Applicants believe correct the grammatical errors in the claims.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as indefinite.

The rejections are overcome by the amendments to claims 1-16.

The Examiner rejects the claims for "omitting essential steps, such omission amounting to a gap between the steps." The apparent omission of steps in the claims, which resulted from poor wording, is corrected by the amendments to the claims, which clarify the recited steps. For example, the amendment to claim 1 clarifies that fibroblasts are inoculated, cultured and killed in a culture vessel, and then the target cells are cultured in the culture vessel. Thus, in the claims, the term "cell"

has been replaced by "target cells" for clarity. The term "target" is introduced to distinguish the fibroblasts (which, of course, are cells) from the cells which are grown after the fibroblasts are inoculated, cultured and killed. This term is introduced for clarity only, and Applicants believe that this does not constitute new matter.

In claim 2, the recitation "at least partially" has been replaced with --50% or more--. Support for this recitation may be found on page 12, lines 23-27.

Claims 4, 6 and 8 have been amended to remove the redundancy by amending "irradiating ~~electromagnetic radiation~~". Claims 5, 7 and 9 have been correspondingly amended.

Applicants have clarified claim 5 by replacing "wherein electromagnetic radiation is" by --wherein said fibroblasts are killed by--. Applicants do not believe that the recitation of "at least two treatments" in claim 8 is indefinite.

Applicants do not believe that the recitation of "repeating one treatment" in claim 6 is indefinite. This recitation requires only that one of the three listed treatments be repeated.

maintain

Claims 1-16 are rejected under 35 U.S.C. 102(b) as anticipated by Green et al. (U.S. Pat. No. 4,016,036).

The rejection is overcome by the amendments, which clarify the claims. Claim 1 has been amended to clarify that fibroblasts are inoculated, cultured and then killed in a culture vessel, and that then target cells are cultured in the culture vessel.

Green describes inoculating and culturing fibroblasts, for example 3T3 cells. However, there is no description of killing the fibroblasts. In the reference, human epidermal cells or other keratinocytes are grown in cultures with fibroblast cells treated to prevent their multiplication

(column 1, line 63). The method also includes growing fibroblasts in the presence of fibroblast cell products (column 1, line 67). Fibroblast cells are treated prior to inoculation to prevent their multiplication, such as with X or gamma rays, ultraviolet irradiation or alkylating agents (column 2, line 57 to column 3, line 5), but this is not killing the cells. Medium conditioned by the 3T3 cells can also be used to grow the keratinocytes.

Thus, Green does not teach killing fibroblasts, and accordingly does not teach a subsequent step of culturing the epidermal cells or other keratinocytes in the culture vessel in which the fibroblasts were killed. Claims 1 to 15 are therefore not anticipated by Green.

Claims 1-9 and 11-15 are rejected under 35 U.S.C. 103(a) as unpatentable over Makitsubo et al. (EP 0 168 217).

The rejection is overcome by the amendments, which clarify the claims.

Makitsubo discloses a method of extracting a tumor necrosis factor-like substance. The Examiner cites page 2, lines 12-31, which disclose a step (a) in which a macrophage cell line of CAMU-3-R or a fibroblast cell line of L-929 are homogeneously killed in culture medium. In step (b), the medium of step (a) is mixed with a tumor cell line and incubated for 48 hours; In step (c), the culture medium containing the killed fibroblast cell line is mixed and incubated with the tumor cell line. In step (d), the killing effect of the fluid in step (c) which contains a macrophage is compared with that containing a fibroblast.

Although Makitsubo does describe culturing and homogeneously killing a fibroblast cell line (L-929), Makitsubo does not disclose or suggest growing the tumor cell line on the culture vessel in which the fibroblast cell line was grown. Rather, Makitsubo discloses mixing the "culture

containing the killed fibroblasts" with the tumor cell line.

The goal of Makitsubo's procedure is clearly stated: "to extract TNS simply and a lot in quantity." (Page 2, line 1). The purpose of homogeneously killing the macrophage or fibroblast in step (a) is clearly to obtain TNS. The purpose of mixing the culture medium containing the killed fibroblast with tumor cells is to assay the culture medium for the "killing effect." (Page 2, line 18). It does not appear to be a goal of Makitsubo to proliferate the tumor cells. ← applicant's argument persuasive

Thus, Makitsubo does not disclose growing any cells in the culture vessel in which the fibroblasts are killed. Since Makitsubo's purpose is only to obtain TNF, and this TNF is found in the medium containing the killed cells, Makitsubo would not appear to be suggesting anything about the culture vessel. Moreover, TNF kills cells and would not be suggested as an agent for proliferating cells. Claims 1-15 are therefore novel and non-obvious over Makitsubo.

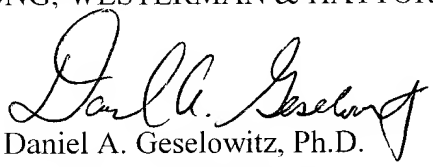
A marked-up version showing the changes made by the present amendment is attached hereto as "Version with Markings to Show Changes Made."

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact Applicant's undersigned agent at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees which may be due with respect to this paper, may be charged to Deposit Account No. 01-2340.

Respectfully submitted,

ARMSTRONG, WESTERMAN & HATTORI, LLP



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend claims 1 - 15 as follows:

1. (Amended) A method for adhering and proliferating ~~cell~~ target cells, which comprises the steps of:

inoculating, culturing and then killing, in a culture vessel, ~~fibroblast~~ fibroblasts derived from a mammal, and then culturing the target cells in said culture vessel.

2. (Amended) The method according to Claim 1, wherein 50% or more of said killed ~~fibroblast is~~ fibroblasts are separated from the culture vessel ~~at least partially~~.

3. (Amended) The method according to Claim 1, wherein said killed ~~fibroblast is~~ fibroblasts are separated from the culture vessel entirely.

4. (Amended) The method according to Claim 1, wherein said ~~fibroblast is~~ fibroblasts are killed by at least one treatment selected from the group consisting of freezing, drying and irradiating ~~electromagnetic radiation~~.

5. (Amended) The method according to Claim ~~4~~ 1, wherein ~~electromagnetic radiation is~~ said fibroblasts are killed by at least one selected from the group consisting of β ray, γ ray, X-ray, electron

beam and UV ray.

6. (Amended) The method according to Claim 1, wherein said ~~fibroblast is killed by~~ killing step of fibroblasts comprises repeating one treatment selected from the group consisting of freezing, drying and irradiating ~~electromagnetic radiation~~.

7. (Amended) The method according to Claim ~~6~~ 1, wherein ~~electromagnetic radiation is~~ said killing step of fibroblasts comprises repeating exposure to at least one selected from the group consisting of β ray, γ ray, electron beam, UV ray and X-ray.

8. (Amended) The method according to Claim 1, wherein said ~~fibroblast is~~ fibroblasts are killed by a combination of at least two treatments selected from the group consisting of freezing, drying and irradiating ~~electromagnetic radiation~~.

9. (Amended) The method according to Claim ~~8~~ 1, wherein ~~electromagnetic radiation is~~ fibroblasts are killed by at least one selected from the group consisting of β ray, γ ray, electron beam, UV ray and X-ray.

10. (Twice Amended) The method according to Claim 1, wherein said ~~fibroblast is~~ fibroblasts are 3T3 mouse embryo ~~fibroblast~~ fibroblasts.

11. (Amended) The method according to Claim 1, wherein said ~~cell is~~ target cells are epithelial ~~cell~~ cells.

12. (Amended) The method according to Claim 11, in which said epithelial ~~cell is~~ cells are epidermal ~~cell~~ cells.

13. (Amended) The method according to Claim 1, wherein said ~~cell is~~ target cells are hepatic ~~cell~~ cells.

14. (Amended) An epidermal cell sheet prepared from ~~the~~ target epidermal ~~cell which is~~ cells cultured using the method according to Claim 1.

15. (Amended) An epidermal cell suspension prepared from ~~the~~ target epidermal ~~cell which is~~ cells cultured using the method according to Claim 1.